Claims

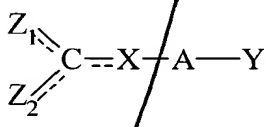
1. A method of increating ATP production in the brain of a subject, comprising administering to a subject an effective amount of a creatine compound and an ATP enhancing agent, such that the ATP production in the brain is increased.

2. The method of claim 1, wherein said creatine compound is creatine.

3. The method of claim 1, wherein said creatine compound is cyclocreatine.

4. The method of claim 1, wherein said creatine compound is creatine phosphate.

5. The method of claim 1, wherein said creatine compound has the formula:



and pharmaceutically acceptable salts thereof, wherein:

a) Y is selected from the group consisting of: $-CO_2H$, -NHOH, $-N0_2$, $-SO_3H$, $-C(=0)NHS0_2J$ and $-P(=O)(OH)(OJ)$, wherein J is selected from the group consisting of: hydrogen, C_1-C_6 straight chain alkyl, C_3-C_6 branched alkyl, C_2-C_6 alkenyl, C_3-C_6 branched alkenyl, and aryl;

b) A is selected from the group consisting of: C, CH, C_1-C_5alkyl, C_2-C_5alkenyl, C_2-C_5alkynyl, and C_1-C_5 alkoyl chain, each having 0-2 substituents which are selected independently from the group consisting of:

1) K, where K is selected from the group consisting of: C_1 -C_6 straight alkyl, C_2-C_6 straight alkenyl, C_1-C_6 straight alkoyl, C_3-C_6 branched alkyl, C_3-C_6 branched alkenyl, and C_4-C_6 branched alkoyl, K having 0-2 substituents independently selected from the group consisting of: bromo, chloro, epoxy and acetoxy;

2) an aryl group selected from the group consisting of: a 1-2 ring carbocycle and a 1-2 ring heterocycle, wherein the aryl group contains 0-2 substituents independently selected from the group consisting of: $-CH_2L$ and $-COCH_2L$ where L is

independently selected from the group consisting of: bromo, chloro, epoxy and acetoxy; and

3) -NH-M, wherein M is selected from the group consisting of: hydrogen, C_1-C_4 alkyl, C_2-C_4 alkenyl, C_1-C_4 alkoyl, C_3-C_4 branched alkyl, C_3-C_4 branched alkenyl, and C_4 branched alkoyl;

c) X is selected from the group consisting of NR_1, CHR_1, CR_1, O and S, wherein R_1 is selected from the group consisting of:

1) hydrogen;

2) K where K is selected from the group consisting of: C_1-C_6 straight alkyl, C_2-C_6 straight alkenyl, C_1-C_6 straight alkoyl, C_3-C_6 branched alkyl, C_3-C_6 branched alkenyl, and C_4-C_6 branched alkoyl, K having 0-2 substituents independently selected from the group consisting of: bromo, chloro, epoxy and acetoxy;

3) an aryl group selected from the group consisting of a 1-2 ring carbocycle and a 1-2 ring heterocycle, wherein the aryl group contains 0-2 substituents independently selected from the group consisting of: $-CH_2L$ and $-COCH_2L$ where L is independently selected from the group consisting of: bromo, chloro, epoxy and acetoxy;

4) a C_5-C_9 a-amino-w-methyl-w-adenosylcarboxylic acid attached via the w-methyl carbon;

5) a C_5-C_9 a-amino-w-aza-w-methyl-w-adenosylcarboxylic acid attached via the w-methyl carbon; and

6) a C_5-C_9 a-amino-w-thia-w-methyl-w-adenosylcarboxylic acid attached via the w-methyl carbon;

d) Z_1 and Z_2 are chosen independently from the group consisting of: =0, $-NHR_2$, $-CH_2R_2$, $-NR_2OH$; wherein Z_1 and Z_2 may not both be =0 and wherein R_2 is selected from the group consisting of:

1) hydrogen;

2) K, where K is selected from the group consisting of: C_1-C_6 straight alkyl; C_2-C_6 straight alkenyl, C_1-C_6 straight alkoyl, C_3-C_6 branched alkyl, C_3-C_6 branched alkenyl, and C_4-C_6 branched alkoyl, K having 0-2 substituents independently selected from the group consisting of: bromo, chloro, epoxy and acetoxy;

3) an aryl group selected from the group consisting of a 1-2 ring carbocycle and a 1-2 ring heterocycle, wherein the aryl group contains 0-2 substituents independently selected from the group consisting of: $-CH_2L$ and $-COCH_2L$ where L is independently selected from the group consisting of: bromo, chloro, epoxy and acetoxy;

4) a C_4-C_8 a-amino-carboxylic acid attached via the w-carbon;

5) B, wherein B is selected from the group consisting of: $-CO_2H$, -NHOH, $-SO_3H$, $-NO_2$, OP(=O)(OH)(OJ) and -P(=O)(OH)(OJ), wherein J is selected from the group consisting of: hydrogen, C_1-C_6 straight alkyl, C_3-C_6 branched alkyl, C_2-C_6 alkenyl, C_3-C_6 branched alkenyl, and aryl, wherein B is optionally connected to the nitrogen via a linker selected from the group consisting of: C_1-C_2 alkyl, C_2 alkenyl, and C_1-C_2 alkoyl;

6) -D-E, wherein D is selected from the group consisting of: C_1-C_3 straight alkyl, C_3 branched alkyl, C_2-C_3 straight alkenyl, C_3 branched alkenyl, C_1-C_3 straight alkoyl, aryl and aroyl; and E is selected from the group consisting of: $-(PO_3)_nNMP$, where n is 0-2 and NMP is ribonucleotide monophosphate connected via the 5'-phosphate, 3'-phosphate or the aromatic ring of the base; $-[P(=O)(OCH_3)(0)]_m$-Q, where m is 0-3 and Q is a ribonucleoside connected via the ribose or the aromatic ring of the base; $-[P(=O)(OH)(CH_2)]_m$-Q, where m is 0-3 and Q is a ribonucleoside connected via the ribose or the aromatic ring of the base; and an aryl group containing 0-3 substituents chosen independently from the group consisting of: Cl, Br, epoxy, acetoxy, -OG, -C(=O)G, and $-CO_2G$, where G is independently selected from the group consisting of: C_1-C_6 straight alkyl, C_2-C_6 straight alkenyl, C_1 -C_6 straight alkoyl, C_3-C_6 branched alkyl, C_3-C_6 branched alkenyl, C_4-C_6 branched alkoyl, wherein E may be attached to any point to D, and if D is alkyl or alkenyl, D may be connected at either or both ends by an amide linkage; and

7) -E, wherein E is selected from the group consisting of $-(PO_3)_nNMP$, where n is 0-2 and NMP is a ribonucleotide monophosphate connected via the 5'-phosphate, 3'-phosphate or the aromatic ring of the base; $-[P(=O)(OCH_3)(0)]_m$-Q,

where m is 0-3 and Q is a ribonucleoside connected via the ribose or the aromatic ring of the base; -[P(=O)(OH)(CH_2)]$_m$-Q, where m is 0-3 and Q is a ribonucleoside connected via the ribose or the aromatic ring of the base; and an aryl group containing 0-3 substituents chose independently from the group consisting of: C_1, Br, epoxy, acetoxy, -OG, -C(=O)G, and -CO=G, where G is independently selected from the group consisting of: C_1-C_6 straight alkyl, C_2-C_6 straight alkenyl, C_1-C_6 straight alkoyl, C_3-C_6 branched alkyl, C_3-C_6 branched alkenyl, C_4-C_6 branched alkoyl; and if E is aryl, E may be connected by an amide linkage;

e) if R_1 and at least one R_2 group are present, R_1 may be connected by a single or double bond to an R_2 group to form a cycle of 5 to 7 members;

f) if two R_2 groups are present, they may be connected by a single or a double bond to form a cycle of 4 to 7 members; and

g) if R_1 is present and Z_1 or Z_2 is selected from the group consisting of -NHR_2, -CH_2R_2 and -NR_2OH, then R_1 may be connected by a single or double bond to the carbon or nitrogen of either Z_1 or Z_2 to form a cycle of 4 to 7 members.

6. The method of claim 1, wherein said ATP enhancing agent is CoQs, vitamins, spin traps, carnitine, antioxidants, sugars, vincopocetine or combinations thereof.

7. The method of claim 6, wherein the agent is CoQ_{10}.

8. The method of claim 6, wherein the agent is carnitine.

9. The method of claim 6, wherein the sugar is ribose.

10. The method of claim 6, wherein said antioxidant is pyruvate.

11. The method of claim 6, wherein the antioxidant is lutein.

12. The method of claim 6, wherein the agent is vinpocetine.

13. The method of claim 1, further comprising administering a herbal extract.

14. The method of claim 13, wherein the extract is rosemary or black caraway extract.

15. The method of claim 1, further comprising administering a berry oil or meal.

16. The method of claim 15, wherein said berry oil or meal is from blackberries, blueberries, black raspberries, or mixtures thereof.

17. The method of claim 1, wherein said subject is suffering or at risk of sufering from a nervous system disorder.

18. The method of claim 1, wherein said subject is human.

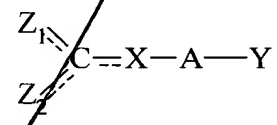
19. A method of preventing nervous system disorders, comprising administering to a subject an effective amount of a creatine compounds and a neuroprotective agent, such that said nervous system disorders are prevented.

20. The method of claim 19, wherein said creatine compound is creatine.

21. The method of claim 19, wherein said creatine compound is cyclocreatine.

22. The method of claim 19, wherein said creatine compound is creatine phosphate.

23. The method of claim 19, wherein said creatine compound has the formula:



and pharmaceutically acceptable salts thereof, wherein:

a) Y is selected from the group consisting of: $-CO_2H$, -NHOH, $-NO_2$, $-SO_3H$, $-C(=O)NHSO_2J$ and $-P(=O)(OH)(OJ)$, wherein J is selected from the group consisting of: hydrogen, C_1-C_6 straight chain alkyl, C_3-C_6 branched alkyl, C_2-C_6 alkenyl, C_3-C_6 branched alkenyl, and aryl;

b) A is selected from the group consisting of: C, CH, C_1-C_5alkyl, C_2-C_5alkenyl, C_2-C_5alkynyl, and C_1-C_5 alkoyl chain, each having 0-2 substituents which are selected independently from the group consisting of:

1) K, where K is selected from the group consisting of: C_1 -C_6 straight alkyl, C_2-C_6 straight alkenyl, C_1-C_6 straight alkoyl, C_3-C_6 branched alkyl, C_3-C_6 branched alkenyl, and C_4-C_6 branched alkoyl, K having 0-2 substituents independently selected from the group consisting of: bromo, chloro, epoxy and acetoxy;

2) an aryl group selected from the group consisting of: a 1-2 ring carbocycle and a 1-2 ring heterocycle, wherein the aryl group contains 0-2 substituents independently selected from the group consisting of: $-CH_2L$ and $-COCH_2L$ where L is independently selected from the group consisting of: bromo, chloro, epoxy and acetoxy; and

3) -NH-M, wherein M is selected from the group consisting of: hydrogen, C_1-C_4 alkyl, C_2-C_4 alkenyl, C_1-C_4 alkoyl, C_3-C_4 branched alkyl, C_3-C_4 branched alkenyl, and C_4 branched alkoyl;

c) X is selected from the group consisting of NR_1, CHR_1, CR_1, O and S, wherein R_1 is selected from the group consisting of:

1) hydrogen;

2) K where K is selected from the group consisting of: C_1-C_6 straight alkyl, C_2-C_6 straight alkenyl, C_1-C_6 straight alkoyl, C_3-C_6 branched alkyl, C_3-C_6 branched alkenyl, and C_4-C_6 branched alkoyl, K having 0-2 substituents independently selected from the group consisting of: bromo, chloro, epoxy and acetoxy;

3) an aryl group selected from the group consisting of a 1-2 ring carbocycle and a 1-2 ring heterocycle, wherein the aryl group contains 0-2 substituents independently selected from the group consisting of: $-CH_2L$ and $-COCH_2L$ where L is independently selected from the group consisting of: bromo, chloro, epoxy and acetoxy;

4) a C_5-C_9 a-amino-w-methyl-w-adenosylcarboxylic acid attached via the w-methyl carbon;

5) a C_5-C_9 a-amino-w-aza-w-methyl-w-adenosylcarboxylic acid attached via the w-methyl carbon; and

6) a C_5-C_9 a-amino-w-thia-w-methyl-w-adenosylcarboxylic acid attached via the w-methyl carbon;

d) Z_1 and Z_2 are chosen independently from the group consisting of: =0, $-NHR_2$, $-CH_2R_2$, $-NR_2OH$; wherein Z_1 and Z_2 may not both be =0 and wherein R_2 is selected from the group consisting of:

1) hydrogen;

2) K, where K is selected from the group consisting of: C_1-C_6 straight alkyl; C_2-C_6 straight alkenyl, C_1-C_6 straight alkoyl, C_3-C_6 branched alkyl, C_3-C_6 branched alkenyl, and C_4-C_6 branched alkoyl, K having 0-2 substituents independently selected from the group consisting of: bromo, chloro, epoxy and acetoxy;

3) an aryl group selected from the group consisting of a 1-2 ring carbocycle and a 1-2 ring heterocycle, wherein the aryl group contains 0-2 substituents independently selected from the group consisting of: $-CH_2L$ and $-COCH_2L$ where L is independently selected from the group consisting of: bromo, chloro, epoxy and acetoxy;

4) a C_4-C_8 a-amino-carboxylic acid attached via the w-carbon;

5) B, wherein B is selected from the group consisting of: $-CO_2H$, -NHOH, $-SO_3H$, $-NO_2$, OP(=O)(OH)(OJ) and -P(=O)(OH)(OJ), wherein J is selected from the group consisting of: hydrogen, C_1-C_6 straight alkyl, C_3-C_6 branched alkyl, C_2-C_6 alkenyl, C_3-C_6 branched alkenyl, and aryl, wherein B is optionally connected to the nitrogen via a linker selected from the group consisting of: C_1-C_2 alkyl, C_2 alkenyl, and C_1-C_2 alkoyl;

6) -D-E, wherein D is selected from the group consisting of: C_1-C_3 straight alkyl, C_3 branched alkyl, C_2-C_3 straight alkenyl, C_3 branched alkenyl, C_1-C_3 straight alkoyl, aryl and aroyl; and E is selected from the group consisting of: $-(PO_3)_nNMP$, where n is 0-2 and NMP is ribonucleotide monophosphate connected via the 5'-phosphate, 3'-phosphate or the aromatic ring of the base; $-[P(=O)(OCH_3)(O)]_m$-Q, where m is 0-3 and Q is a ribonucleoside connected via the ribose or the aromatic ring of

the base; -$[P(=O)(OH)(CH_2)]_m$-Q, where m is 0-3 and Q is a ribonucleoside connected via the ribose or the aromatic ring of the base; and an aryl group containing 0-3 substituents chosen independently from the group consisting of: Cl, Br, epoxy, acetoxy, -OG, -C(=O)G, and -CO_2G, where G is independently selected from the group consisting of: C_1-C_6 straight alkyl, C_2-C_6 straight alkenyl, C_1 -C_6 straight alkoyl, C_3-C_6 branched alkyl, C_3-C_6 branched alkenyl, C_4-C_6 branched alkoyl, wherein E may be attached to any point to D, and if D is alkyl or alkenyl, D may be connected at either or both ends by an amide linkage; and

7) -E, wherein E is selected from the group consisting of -$(PO_3)_n$NMP, where n is 0-2 and NMP is a ribonucleotide monophosphate connected via the 5'-phosphate, 3'-phosphate or the aromatic ring of the base; -$[P(=O)(OCH_3)(0)]_m$-Q, where m is 0-3 and Q is a ribonucleoside connected via the ribose or the aromatic ring of the base; -$[P(=O)(OH)(CH_2)]_m$-Q, where m is 0-3 and Q is a ribonucleoside connected via the ribose or the aromatic ring of the base; and an aryl group containing 0-3 substituents chose independently from the group consisting of: C_1, Br, epoxy, acetoxy, -OG, -C(=O)G, and -CO=G, where G is independently selected from the group consisting of: C_1-C_6 straight alkyl, C_2-C_6 straight alkenyl, C_1-C_6 straight alkoyl, C_3-C_6 branched alkyl, C_3-C_6 branched alkenyl, C_4-C_6 branched alkoyl; and if E is aryl, E may be connected by an amide linkage;

e) if R_1 and at least one R_2 group are present, R_1 may be connected by a single or double bond to an R_2 group to form a cycle of 5 to 7 members;

f) if two R_2 groups are present, they may be connected by a single or a double bond to form a cycle of 4 to 7 members; and

g) if R_1 is present and Z_1 or Z_2 is selected from the group consisting of -NHR_2, -CH_2R_2 and -NR_2OH, then R_1 may be connected by a single or double bond to the carbon or nitrogen of either Z_1 or Z_2 to form a cycle of 4 to 7 members.

24. The method of claim 19, wherein said nervous system disorder is selected from the group consisting of Alzheimer's, ALS, Huntington's, Multiple Sclerosis, and aging.

25. The method of claim 19, wherein said neuroprotective agent is selected from the group consisting of approved drugs for the prevention or treatment of neurodegenerative diseases, inhibitors of glutamate excitotoxicity, growth factors, nitric oxide synthase

inhibitors, cyclooxygenase 2 inhibitors, aspirin, ICE inhibitors, neuroimmunophilis, N-acetylcystene, antioxidants, vinpocetine, fatty acids, lipoic acid, vitamins, cofactors, and CoQ_{10}.

26. The method of claim 25, wherein the agent is CoQ_{10}.

27. The method of claim 25, wherein the fatty acid is docosahexanoic acid.

28. The method of claim 25, wherein the fatty acid is eicosapentenoic acid.

29. The method of claim 25, wherein the fatty acid is gamma linolenic acid.

30. The method of claim 25, further comprising administering a herbal extract.

31. The method of claim 30, wherein the extract is rosemary or black caraway extract.

32. The method of claim 19, further comprising administering a berry oil or meal.

33. The method of claim 32, wherein said berry oil or meal is from blackberries, blueberries, black raspberries, or mixtures thereof.

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34. A method of protecting the nervous system of a subject against oxidative damage, comprising administering to said subject an effective amount of a creatine compound and a neuroprotective agent, such that the nervous system of the subject is protected against oxidative damage.

35. The method of claim 34, wherein said creatine compound is creatine.

36. The method of claim 34, wherein said creatine compound is cyclocreatine.

37. The method of claim 34, wherein said creatine compound is creatine phosphate.

38. The method of claim 34, wherein said neuroprotective agent is an anti-oxidant compound.

39. The method of claim 38, wherein said anti-oxidant is selected from the group consisting of vitamin E, lutein, pyruvate, alpha-omega fatty acids, BHP, alpha-lipoate, thioctic acid, 1,2-dithiolane-3-pentanoic acid, 1,2-dithiolane-3 valeric acid, and 6,8-dithiooctanoic acid.

40. A method of treating a subject suffering from a nervous system disorder, comprising administering to said subject a creatine kinase modulating compound which enhances ATP production and a neuroprotective agent, such that said nervous system disorder is treated.

41. The method of claim 40, wherein said creatine kinase modulating compound is a creatine compound.

42. The method of claim 40, wherein said creatine compound is creatine.

43. The method of claim 40 wherein said creatine compound is creatine phosphate.

44. The method of claim 40, wherein said creatine compound is cyclocreatine.

45. The method of claim 40, wherein said subject is suffering from a nervous system disorder selected from the group consisting of Alzheimer's, Multiple Sclerosis, ALS, or Huntington's disease.

46. The method of claim 45, wherein said neuroprotective agent is selected from the group consisting of approved drugs for the prevention or treatment of neurodegenerative diseases, inhibitors of glutamate excitotoxicity, growth factors, nitric oxide synthase inhibitors, cyclooxygenase 2 inhibitors, aspirin, ICE inhibitors, neuroimmunophilis, N-acetylcystene, antioxidants, vinpocetine. fatty acids, lipoic acid, vitamins, cofactors, and CoQ_{10}.

47. A method for protecting the nervous system against nervous system disease states comprising administering to a subject a dietary food supplement comprising a creatine compound and a neuroprotective agent.

48. The method of claim 47, wherein said method enhances nervous system activities.

49. The method of claim 48, wherein said nervous system activity is memory.

50. The method of claim 47, wherein said nervous system disease is Alzheimer's, Multiple Sclerosis, ALS, aging, or Huntington's disease.

51. The method of claim 47, wherein said neuroprotective agent is selected from the group consisting of approved drugs for the prevention or treatment of neurodegenerative diseases, inhibitors of glutamate excitotoxicity, growth factors, nitric oxide synthase inhibitors, cyclooxygenase 2 inhibitors, aspirin, ICE inhibitors, neuroimmunophilis, N-acetylcystene, antioxidants, vinpocetine. fatty acids, lipoic acid, vitamins, cofactors, and CoQ_{10}.

52. The method of claim 47, further comprising administering a herbal extract.

53. The method of claim 52, wherein the extract is rosemary or black caraway extract.

54. The method of claim 47, further comprising administering a berry oil or meal.

55. The method of claim 54, wherein said berry oil or meal is from blackberries, blueberries, black raspberries, or mixtures thereof.

56. A method for treating memory impairment in a subject, comprising administering to said subject an effective amount of a creatine kinase modulating compound and a neuroprotective agent, such that said memory impairment is treated in said subject

57. The method of claim 56, wherein said subject is administered a creatine kinase modulating compound to prevent memory impairment.

58. The method of claim 56, wherein said subject is suffering from Alzheimer's disease, ALS, or Huntington's disease.

59. The method of claim 56, wherein said creatine kinase modulating compound is a creatine compound.

60. The method of claim 59, wherein said creatine compound is creatine.

61. The method of claim 59, wherein said creatine compound is creatine phosphate.

62. The method of claim 59, wherein said creatine compound is cyclocreatine.

63. The method of claim 56, wherein said neuroprotective agent is selected from the group consisting of approved drugs for the prevention or treatment of neurodegenerative diseases, inhibitors of glutamate excitotoxicity, growth factors, nitric oxide synthase inhibitors, cyclooxygenase 2 inhibitors, aspirin, ICE inhibitors, neuroimmunophilis, N-acetylcystene, antioxidants, vinpocetine. fatty acids, lipoic acid, vitamins, cofactors, and CoQ_{10}.

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